

Review Article

Open Access

Goran P. Koraćević, Sonja S. Dakić, Radmila M. Veličković-Radovanović, Svetlana R. Apostolović, Nebojša H. Krstić, Ivan S. Tasić, Marija D. Zdravković, Nebojša M. Antonijević, Goran N. Damjanović, Tomislav L. Kostić

Amlodipine as an antiischemic drug is superior to long acting nitrates

Abstract: European Society of Cardiology Guidelines cite results of meta-analysis that the use of calcium channel blockers results in fewer angina episodes per week vs. long-acting nitrates. Moreover, we listed 12 reasons more to prefer amlodipine over long-acting nitrates, especially in stable angina pectoris patients with arterial hypertension. It may be the way to decrease polypharmacy without losing efficacy. Some important advantages of amlodipine versus long-acting nitrate(s) are: amlodipine also treats hypertension, it helps reducing hypertensive target

organ damages (e.g. left ventricular hypertrophy) and prevents morning blood pressure surge. Moreover, amlodipine can be given once daily (which improves adherence), it produces neither tolerance nor rebound, it has less side effects.

Keywords: Amlodipine, Long acting nitrates, Stable angina pectoris

DOI 10.1515/med-2015-0011

Received: October 2, 2013; accepted: April 1, 2014

***Corresponding author: Sonja S. Dakić:** Department for Cardiovascular Diseases, Clinical center Niš, Bulevar Dr Z.Djindjića 48, 18000 Niš, Serbia, E-mail: sonjadakic@yahoo.com

Goran P. Koraćević: Department for Cardiovascular Diseases, Clinical center Niš, Bulevar Dr Z.Djindjića 48, 18000 Niš, Serbia, Medical Faculty, University of Niš, Bulevar Dr Zorana Djindjića 81, 18000 Niš, Serbia

Radmila M. Veličković-Radovanović: Medical Faculty, University of Niš, Bulevar Dr Zorana Djindjića 81, 18000 Niš, Serbia
Department of Clinical Pharmacology, Clinical center Niš, Bulevar Dr Zorana Djindjića 48, 18000 Serbia

Svetlana R. Apostolović: Department for Cardiovascular Diseases, Clinical center Niš, Bulevar Dr Z.Djindjića 48, 18000 Niš, Serbia, Medical Faculty, University of Niš, Bulevar Dr Zorana Djindjića 81, 18000 Niš, Serbia

Nebojša H. Krstić: Department for Cardiovascular Diseases, Clinical center Niš, Bulevar Dr Z.Djindjića 48, 18000 Niš, Serbia

Ivan S. Tasić: Department for Cardiovascular Diseases, Clinical center Niš, Bulevar Dr Z.Djindjića 48, 18000 Niš, Serbia
Institute for therapy and prevention Niška Banja, Srpskih junaka 2, 18205 Niška Banja, Serbia

Marija D. Zdravković: Clinical Hospital Center Bežanijska kosa, Faculty of Medicine, University of Belgrade, Bežanijska kosa bb, 11000 Belgrade, Serbia

Nebojša M. Antonijević: School of Medicine, Belgrade, Clinic of Cardiology, Clinical Centre of Serbia, Pasterova 2, 11000 Belgrade, Serbia

Goran N. Damjanović: Military Hospital Niš, Bulevar Dr Zorana Đinđića bb, 18000 Niš, Serbia

Tomislav L. Kostić: Department for Cardiovascular Diseases, Clinical center Niš, Bulevar Dr Z.Djindjića 48, 18000 Niš, Serbia

1 Introduction

Many patients have both coronary artery disease (CAD) and arterial hypertension (HTN). Both diseases become far more frequent with aging. Moreover, HTN is the most common coexisting cardiovascular risk factor with CAD [1]. It is more important to control blood pressure (BP) in patients with established cardiovascular disease [2]. Following beta-blockers, nitrates and calcium channel blockers (CCBs) are the main antiischemic drugs [1-4].

Since the first reports of the antiischemic action of amlodipine in humans, much more evidence has been accumulated from important studies: double-blind Circadian Anti-ischemia Program in Europe (CAPE), the Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study, Coronary Angioplasty amlodipine RESTenosis Study (CAPARES), The Valsartan Antihypertensive Long-term Use Evaluation (VALUE), Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH), Prevention of Recurrent Venous Thromboembolism (PREVENT) [5].

Due to the impression that the full antiischemic potential of the drug has neither been recognized nor utilized,



the aim of this (narrative) review is to analyze the value of amlodipine versus long-acting nitrates (LAN) in the therapy of stable CAD.

2 Attempt to do systematic review

A PubMed search (March, 15th 2013) for „amlodipine *nitrate* randomized clinical trial“ resulted in only 22 items. Among them, only one is completely relevant to the topic [6]. Another refers to a specific form of angina pectoris (AP), e.g., (cardiac) syndrome X [7]. Moreover, a PubMed search (on the same date) for „amlodipine *mononitrate* randomized clinical trial“ resulted in 4 papers, with only one important for the present analysis [8]. Furthermore, a PubMed search for „amlodipine *dinitrate* randomized clinical trial“ retrieved 7 papers, and one of them is relevant [9].

Thus searching in one of the most frequently used and cited database for „head-to-head“ comparisons of amlodipine and long acting nitrate(s) in randomized controlled trials (RCTs), as far as the antiischemic effect is concerned, resulted in only 3 relevant papers. thus, a systematic analysis did not seem adequate, and we proceeded to a narrative review, using three aforementioned trials results.

2.1 Amlodipine does another job –antihypertensive treatment, but nitrates do not

HTN is the most important risk factor for cardiovascular diseases (CVD). If uncontrolled, HTN decreases the life-span and leads to disabling complications, such as stroke and heart failure. These complications can be largely prevented by proper antihypertensive treatment [10, 11].

Amlodipine is a first-line antihypertensive drug, and many trials have demonstrated its usefulness, including but not limited to the Anglo-Cardiff Collaborative Trial (ACCT), ASCOT [10, 11]. Moreover, eleven trials studied ambulatory BP in HTN patients and showed that 24 hours (24-h) BP reduction with calcium channel blockers (CCBs) was greater than that with other antihypertensive drugs. The weighted mean difference was 5 mmHg for systolic and 3 mmHg for diastolic BP. The authors of a scientific statement from the Asian Pacific Heart Association suggested, that CCBs provided superior protection against stroke and that some agents, such as amlodipine, also provided similar protection against myocardial infarction. They recommended CCB as a preferred drug for the

therapy of HTN in the Eastern Asian region to improve BP control and to confront the aggravating epidemic of stroke and CAD [12].

On the other hand, LAN can not be used in the therapy of HTN: it leads either to insufficient control of HTN and complications such as stroke, heart failure, or to the necessity to add more drugs, producing a polypharmacy. The polypharmacy has the possibility to produce other complications, indeed.

2.2 Amlodipine does another job: it treats Target Organ Damages (TOD) in HTN, but nitrates do not

Amlodipine treats TOD in HTN, e.g., left ventricular hypertrophy (LVH). This is very important because hypertensive LVH has been shown to be marker of worse prognosis [10]. The Framingham Heart Study showed that prevalence of LVH increases with age ($P < 0.001$), with 33% of men and 49% of women age 70 or older affected. A significant association between BP and LVH is present and occurs at levels of systolic pressure below 140 mmHg [13]. For example, a relatively short treatment (2 years) with amlodipine decreased LV mass and improved diastolic function [14, 15].

A large study, The Losartan Intervention For Endpoint reduction (LIFE) study, showed that reduction in LV mass induced by amlodipine is significantly and independently associated with reduction of major cardiovascular events, stroke and cardiovascular and all-cause mortality [10]. Moreover, there is evidence from the ACCOMPLISH trial that not only LVH but also nephropathy may improve with amlodipine. Namely, a benazepril plus amlodipine combination should be considered in preference to benazepril plus hydrochlorothiazide because the former combination slows progression of nephropathy to a greater extent [16].

CCBs can also reduce progression of carotid hypertrophy and atherosclerosis and have a superior effect on HTN-related thickening of the carotid artery compared with that of other antihypertensive drugs [10]. CCBs are particularly useful in stroke prevention, which is very important in older patients, who are the typical patients with both CAD and HTN.

2.3 Amlodipine controls morning BP surge, but nitrates do not

The BP surge occurs between 6 AM and noon: 10–30 mmHg in systolic BP and 7–23 mmHg in diastolic BP [17]. The BP

surge coincides with an increase in pulse rate, sympathetic tone, and activation of the rennin-angiotensin system (RAS) and is associated with a peak in the incidence of cardiovascular (CV) events and sudden death [18]. Thus, unwanted cardiac events are much more common in the first few hours after awakening, which led to the memorable title and message of an editorial: “Should we get up in the morning?” [19]. Amlodipine has a consistent 24-hour (24h) antihypertensive effect and is potent in decreasing the rate of early morning BP increase.

Effects of the long-acting angiotensin-converting enzyme (ACE) inhibitor (temocapril) were compared with long acting CCB (amlodipine) on 24-h ambulatory BP in elderly hypertensive patients. Amlodipine showed stronger antihypertensive effect in the night time and morning, especially in non-dippers [20].

2.4 Amlodipine has a better risk/benefit ratio vs. nitrates (in direct comparative studies)

Once daily amlodipine 5–10 mg provides significantly better control of stable angina than isosorbide mononitrate 25–50 mg once daily in a RCT of 97 elderly patients, studied at Hammersmith Hospital, London [6]. Moreover, amlodipine (5–10 mg once-daily) was more effective than sustained-release isosorbide dinitrate (two daily doses of 40 mg) as monotherapy in RCT of 59 patients with chronic stable AP [9].

Combination therapy of amlodipine and atenolol in RCT CAPE-II trial also reduced ischemia and was superior to isosorbide 5-mononitrate and diltiazem, especially during the drug-free interval with maintenance of ischemia reduction [21].

Long-term treatment with LAN may produce less favorable effects on coronary endothelial function and the constrictive response to acetylcholine when compared with long-acting CCBs; this has also been used for the treatment of AP [22].

This agrees with the suggestion that amlodipine is particularly helpful in HTN patients [4].

2.5 Amlodipine has pleiotropic effects (like statins and ACEI/ARB), but nitrates do not

In addition to its BP-lowering effects, amlodipine shows vasoprotective effects (pleiotropic effects) [23]. The

Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation (NORMALISE) was the first clinical study showing that antihypertensive treatment with amlodipine is associated with slowing of coronary atherosclerosis progression and reduced incidence of CV events [24]. Among other factors, inflammation and oxidation are involved in progression of atherosclerosis and new lesion development [25]. Inhibition of the atherosclerotic formation by amlodipine is correlated with its inhibitory actions toward oxidative stress, inflammation and the production of adhesive molecules [26]. Amlodipine exerts also antiproliferative effects on coronary artery smooth muscle cells that are involved in the progression of atherosclerosis [27]. Moreover, amlodipine is known to stimulate nitric oxide (NO) production from endothelial cells, and endothelial nitric oxide synthase (eNOS) activation is independent of other pleiotropic effects of the CCB, such as superoxide anion scavenging and ACE inhibition [28].

The combination of amlodipine and atorvastatin produced an additional 60% reduction of atherosclerosis compared with that observed using the statin alone. The combination of these two drugs showed synergistic effects on acute NO release/endothelial function, and additive effects in the improvement of arterial compliance in hypertensive hyperlipidaemic patients [25].

2.6 Amlodipine can be given once daily, but nitrates can not, which translates into the better adherence vs. nitrates

Amlodipine has a long duration of action (plasma half-life is 30–50h), a very good trough-to-peak ratio, and it can be given once daily [2, 18]. If one or two doses are missed, amlodipine maintains a significant and important antihypertensive effect with the trough-to-peak ratio still over 50% 72-h after the last active dose [29]. Long-acting drugs that have the ability to lower BP over a 24-h period with once per day administration, make the antihypertensive effect more homogeneous over the 24-h and minimize BP variability. It is pragmatically important so that drugs should have preference [29].

The anti-ischemic action of amlodipine was maintained for more than 24-h after the last dose, meaning that it provides both better efficacy (by covering the entire 24-h period) and better compliance (by tolerating a dose omission of several hours) [30].

2.7 Single-pill combination of amlodipine and another drug, useful in CAD, is available, but LAN has no such combination

Many hypertensive patients require three or more medications. Drugs having complementary actions or having an improved adverse effect profile can be combined [31].

Fixed-dose combination treatments using an ACE inhibitor, such as perindopril, plus a CCB, such as amlodipine, improve BP control and CV outcomes in hypertensive patients. This treatment is well tolerated and well adhered to by patients [32]. Amlodipine can also be combined with an angiotensin receptor blocker (ARB). Amlodipine plus olmesartan provides significant lowering of BP [33]. Thus, the combinations of amlodipine and ACEi / ARB is additionally beneficial in CAD patients, while preserving adherence. Such combinations with LAN simply do not exist.

2.8 Amlodipine has fewer side-effects than nitrates

Amlodipine is generally well tolerated; mild to moderate edema is most common adverse effect [11]. Adverse events are more frequent with isosorbide dinitrate than with amlodipine ($P < 0.02$) [9].

In one study, isosorbide mononitrate produced more side-effects in comparison with amlodipine (46% versus 15%, $P = 0.008$) [8].

2.9 Amlodipine does not produce (such) an increase in heart rate as do nitrates

It has been well-recognized that LAN increase the heart rate (by the activation of sympathetic nervous system, due to vasodilation) [1, 3]. After single dose of amlodipine, BP decreases gradually over 4–8h and may slowly return to baseline over 24–72h. After oral administration, the drug is absorbed gradually, binds to target receptors in a slow, sustained fashion, and produces a gradual vasodilation, reducing the incidence of side effects (such as reflex tachycardia and headache, which can be troublesome with other CCBs) [4], [34–37]. The antihypertensive effect of amlodipine is not accompanied by an increase in sympathetic activity or activation of the RAS [38, 39]. Diurnal patterns of plasma noradrenaline levels and renin activity 1, 4, and 7 days after the start of therapy with amlodipine were unchanged [38]. It is also important that discontinuation of amlodipine treatment is accompanied by slow

return of BP to baseline over 7–10 days, with no evidence of a “rebound” effect. [36, 40, 41]. In rats, reflex tachycardia occurred only after the application of high doses of amlodipine [42]. Some authors have shown that amlodipine has an impact on autonomic modulation as a shift to sympathetic hyperactivity; however, this observation did not reach statistical significance. In a group of patients with vagal predominance, amlodipine increased sympathetic and decreased vagal activity. Amlodipine mostly affects autonomic function modulation in patients with vagal predominance [43].

On the basis of all the above-mentioned, it can be concluded that using amlodipine in proper doses in anti-hypertensive therapy can avoid sudden hypotension, which is responsible for an increase in 24-h BP variability and reflex tachycardia, two phenomena that have an unfavorable impact on prognosis in hypertensive patients [34], [44–47].

2.10 Amlodipine does not produce tolerance, but nitrates do

Tolerance is the major problem with the use of nitrates [2]. Nitrate tolerance, the loss of vascular responsiveness with continued use of nitrates, means that these drugs gradually lose their effect, both in heart failure and in AP [48]. “Monday morning headache” was noticed a century ago in workers in nitroglycerin (NTG) manufacturing facilities: regular exposure to NTG in the workplace used to lead to the development of NTG tolerance (as far as the vasodilating effects are concerned) and headache disappeared. Over the weekend the workers lost the tolerance to NTG and when they were re-exposed on Monday, the prominent vasodilation produced tachycardia, dizziness, and a headache.

Nitrate tolerance may develop when nitrate levels are continuously higher than a certain threshold level, which results in decreased protection against AP attacks and resistance to the short-acting NTG. It is necessary to maintain a daily nitrate-free interval of 10–14h to avoid development of nitrate tolerance [3].

Thus, a nitrate-free interval is needed each day, but then nitrate rebound may occur [49]. Generally, if dosing frequency is greater than once daily, the intervals between doses can vary and may be protracted. It can be presented in a few ways: the form of drug holidays when dosing is omitted for one or more days, usually followed by a resumption of full-strength dosing, resulting in excessive drug effects, rebound effects when therapy is suddenly stopped, and a period without effective drug action. Poor

compliance has also financial consequences due to more frequent hospitalisations [50]. Because of some characteristics such as concentration-time profiles and duration of action, amlodipine can provide better therapeutic coverage than other drugs that have a shorter duration of action. As it has been mentioned, the antihypertensive efficacy of amlodipine persists after 2 „missed doses“ [50, 51]. There is no recorded evidence of tolerance to amlodipine over 3 months, and any significant problem associated with its withdrawal [52].

2.11 Amlodipine *does not produce rebound*, but nitrates do

Nitrates have a rebound phenomenon during a nitrate-free interval: diminished anginal threshold increase in the number and intensity of AP attacks (“rebound angina”) [49]. The rebound phenomenon in nitrates was also noticed a century ago in munitions workers handling a NTG-cellulose mixture attacks of AP; sudden deaths occurred most frequently during brief periods away from work, in particular on Sunday nights or Monday mornings. That occurs because withdrawal of coronary vasodilators cause vasoconstriction with acute hypertension. Following sudden cease of large doses of nitrates, AP is intensified due to increased sensitivity to vasoconstrictor stimuli [2].

Patients should know that abruptly discontinued LAN may lead to intensification of their AP [3].

Gradual onset of action and long half-life of amlodipine can help avoid withdrawal effects such as the exacerbation of AP and precipitation of myocardial infarction, as the case with beta blockers [53]. Amlodipine in stable AP has sustained efficacy and lack of “withdrawal phenomenon” upon abrupt discontinuation (of the type noted with abrupt beta blocker cessation) [52]. „Rebounds“ (clinical worsening following the abrupt cessation of the drug therapy) are well known for beta-blockers and nitrates. If there is nitrate rebound and beta-blocker rebound at the same time, it can be even life threatening for the patient. It is important that there is at least one long-acting anti-ischaemic drug such as amlodipine. For example, if the patient misses a morning dose of beta-blocker and LAN, it can be risky, but if the patient misses a morning dose of beta-blocker, he/she is covered by the amlodipine that he/she took the night before. It is less possible that the patient miss both evening and morning dose [54].

2.12 Amlodipine *can be combined with phosphodiesterase-5 inhibitors (Sildenafil and Cialis), but nitrates can not*

Phosphodiesterase-5 (PDE-5) inhibitors are selective blockers of PDE-5, and they catalyze the hydrolysis of cyclic guanosine monophosphate (cGMP) to its corresponding monophosphates. cGMP is a potent vasodilator and NO donor [55].

Recent studies have shown several beneficial pleiotropic cardiovascular effects of PDE-5 inhibitors in patients with erectile dysfunction and multiple comorbidities, such as CAD, heart failure, hypertension, and diabetes mellitus. The use of PDE-5 inhibitors in these patients has been very effective, safe, and well tolerated. Drug interactions have been minimal, except for nitrates. Their interaction may result in severe vasodilation and hypotension [2, 55, 56]. If a patient takes organic nitrates (in any form, either regularly and/or intermittently), co-administration of sildenafil is contraindicated [56]. Co-administration of the PDE-5 inhibitors sildenafil, tadalafil, or vardenafil with nitrate should be strictly avoided within 24-h of nitrate administration because of the risk of profound hypotension [3]. Coadministration of sildenafil did not significantly affect the pharmacokinetics of amlodipine [56]. There are some possible, but not yet confirmed, advantages. For example, amlodipine (possibly by prevention of the calcium overload) can attenuate myocardial postischemic LV dysfunction (myocardial stunning) in comaprison with isosorbide mononitrate. It might be the 13th advantage of amlodipine [8].

Thus, the question: „Which antiischemic drug is better for stable CAD patients with HTN, amlodipine or LAN?“ may be asked also the other way round: «Which drug is better for patients with HTN and CAD?» Guidelines for HTN do not suggest nitrates, indeed.

3 Conclusion

RCTs comparing antischemic efficacy of amlodipine and long-acting nitrate are surprisingly rare, disproportionate to the paramount importance of CAD worldwide. ESC Guidelines cite results of meta-analysis that the use of CCBs results in fewer angina episodes per week vs. long-acting nitrates. Moreover, we have listed here 12 more reasons to prefer amlodipine over long-acting nitrates, especially in stable AP patients with HTN. It may be the way to decrease polypharmacy without losing efficacy.

Acknowledgement: None

Conflict of interest statement: Authors state no conflict of interest

References

- [1] Gayet J.L., Paganelli F., Cohen-Solal A., Update on the medical treatment of stable angina, *Arch Cardiovasc Dis.*, 2011, 104(10), 536-544
- [2] Morrow D., Gersh B., Chronic coronary artery disease, In: Libby P., Bonow R., Mann D., Zipes D. (Eds), *Braunwald's heart disease: A textbook of Cardiovascular Medicine*, 8th ed., Saunders Elsevier, Philadelphia, 2007
- [3] Fihn S.D., Gardin J.M., Abrams J., Berra K., Blankenship J.C., Dallas A.P., et al., 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, *J Am Coll Cardiol.*, 2012, 60(24), 2564-2603
- [4] Parker J.D., Parker J.O., Stable angina pectoris: the medical management of symptomatic myocardial ischemia, *Can J Cardiol.*, 2012, 28(2 Suppl), S70-80
- [5] Jackson N.C., Lee P.S., Reynolds G., Fraix M., Taylor S.H., Improvement of treadmill time to angina by amlodipine, *Br J Clin Pharmacol.*, 1985, 20, 248
- [6] Hall R., Chong C., A double-blind, parallel-group study of amlodipine versus long-acting nitrate in the management of elderly patients with stable angina, *Cardiology*, 2001, 96(2), 72-77
- [7] Lanza G.A., Colonna G., Pasceri V., Maseri A., Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X, *Am J Cardiol.*, 1999, 84(7), 854-856, A8
- [8] Rinaldi C.A., Linka A.Z., Masani N.D., Avery P.G., Jones E., Saunders H., et al., Randomized, double-blind crossover study to investigate the effects of amlodipine and isosorbide mononitrate on the time course and severity of exercise-induced myocardial stunning, *Circulation*, 1998, 25, 98(8), 749-756
- [9] Steffensen R., Melchior T., Bech J., Nissen H., Haastrup B., Grande P., et al., Effects of amlodipine and isosorbide dinitrate on exercise-induced and ambulatory ischemia in patients with chronic stable angina pectoris, *Cardiovasc Drugs Ther.*, 1997, 11(5), 629-635
- [10] Mancia G., de Backer G., Dominiczak A., Cifkova R., Fagard R., Germano G., Guidelines for the management for arterial hypertension]: executive summary: The Task Force on Management of Arterial Hypertension of European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), *Eur Heart J.*, 2007, 28, 1462-1536
- [11] Kloner R.A., Sowers J.R., DiBona G.F., Gaffney M., Wein M., Sex- and age- related antihypertensive effects of amlodipine. The amlodipine Cardiovascular Community Trial Study Group, *Am J Cardiol.*, 1996, 77, 713-722
- [12] Wang J.G., Kario K., Lan T., Wei Y.Q., Park C.G., Kim C.H., et al., Asian Pacific Heart Association. Use of dihydropyridine calcium channel blockers in the management of hypertension in Eastern Asians: a scientific statement from the Asian Pacific Heart Association, *Hypertens Res.*, 2011, 34(4), 423-430
- [13] Levy D., Anderson K.M., Savage D.D., Kannel W.B., Christiansen J.C., Castelli W.P., Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study, *Ann Intern Med.*, 1988, 108(1), 7-13
- [14] Terpstra W.F., May J.F., Smit A.J., de Graeff P.A., Havinga T.K., van den Veur E., et al., Long-term effects of amlodipine and lisinopril on left ventricular mass and diastolic function in elderly, previously untreated hypertensive patients: the ELVERA trial, *J Hypertens.*, 2001, 19(2), 303-309
- [15] Islim I.F., Watson R.D., Ihenacho H.N., Ebanks M., Singh S.P., Amlodipine: effective for treatment of mild to moderate essential hypertension and left ventricular hypertrophy, *Cardiology*, 2001, 96 Suppl 1, 10-18
- [16] Bakris G.L., Sarafidis P.A., Weir M.R., Dahlöf B., Pitt B., Jamerson K., Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial, *Lancet*, 2010, 375(9721), 1173-1181
- [17] Lacourcière Y., Crikelair N., Glazer R.D., Yen J., Calhoun D.A., 24-Hour ambulatory blood pressure control with triple-therapy amlodipine, valsartan and hydrochlorothiazide in patients with moderate to severe hypertension, *J Hum Hypertens.*, 2011, 25, 615-622
- [18] Parati G., Schumacher H., Bilo G., Manica G., Evaluating 24-h antihypertensive efficacy by the smoothness index. A meta-analysis of an ambulatory blood pressure monitoring database, *J Hypertens.*, 2010, 28, 2177-2183
- [19] Mulcahy D., Purcell H., Fox K., Should we get up in the morning? Observations on circadian variations in cardiac events, *Br Heart J.*, 1991, 65(6), 299-301
- [20] Eguchi K., Kario K., Shimada K., Effects of long-acting ACE inhibitor (temocapril) and long-acting Ca channel blocker (amlodipine) on 24-h ambulatory BP in elderly hypertensive patients, *J Hum Hypertens.*, 2001, 15, 64
- [21] Deanfield J.E., Detry J.M., Selliner P., Lichtlen P.R., Thaulow E., Bultas J., et al., Medical treatment of myocardial ischemia in coronary artery disease: effect of drug regime and irregular dosing in the CAPE II trial, *J Am Coll Cardiol.*, 2002, 40, 917-925
- [22] Ninomiya Y., Hamasaki S., Saihara K., Ishida S., Kataoka T., Ogawa M., et al., Comparison of effect between nitrates and calcium channel antagonist on vascular function in patients with normal or mildly diseased coronary arteries, *Heart Vessels*, 2008, 23(2), 83-90
- [23] Preston Mason R., Pleiotropic effects of calcium channel blockers, *Curr Hypertens Rep.*, 2012, 14(4), 293-303
- [24] Nissen S.E., Tuzcu E.M., Libby P., Thompson P.D., Ghali M., Garza D., et al., Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomised controlled trial, *JAMA*, 2004, 292(18), 2217-2225
- [25] Jukema J.W., van der Hoorn J.W., Amlodipine and atorvastatin in atherosclerosis: a review of the potential of combination therapy, *Expert Opin Pharmacother.*, 2004, 5(2), 459-468
- [26] Toba H., Nakagawa Y., Miki S., Shimizu T., Yoshimura A., Inoue R., et al., Calcium channel blockades exhibit anti-inflammatory and antioxidative effects by augmentation of endothelial nitric

- oxide synthase and the inhibition of angiotensin converting enzyme in the N(G)-nitro-L-arginine methyl ester-induced hypertensive rat aorta: vasoprotective effects beyond the blood pressure-lowering effects of amlodipine and manidipine, *Hypertens Res.*, 2005, 28(8), 689-700
- [27] Ohba T., Watanabe H., Murakami M., Radovanovic M., Ilno K., Ishida M., et al., Amlodipine inhibits cell proliferation via PKD1-related pathway, *Biochem Biophys Res Commun.*, 2008, 369(2), 376-381
- [28] Batova S., De Wever J., Godfraind T., Balligand J.L., Dessy C., Feron O., The Calcium channel blocker amlodipine promotes the unclamping of eNOS from caveolin in endothelial cells, *Cardiovasc Res.*, 2006, 71(3), 478-485
- [29] Hernández R.S., Armas-Hernández M.J., Chourio J.A., Armas-Padilla M.C., López L., Alvares M., et al., Comparative effects of amlodipine and nifedipine GITS during treatment and after missing two doses, *Blood Press Monit.*, 2001, 6(1), 47-57
- [30] Marchand X., Tibi T., Bernaud C., Morand P., Evaluation of amlodipine in stable effort angina. Comparison with diltiazem in terms of efficacy, tolerability and maintenance of the antiischemic action 24 hours after the last dose, *Ann Cardiol Angeiol.*, 1996, 45(2), 74-82
- [31] Taylor A.A., Ragbir S., Three in one: safety, efficacy, and patient acceptability of triple fixed-dose combination medicine in the management of hypertension, *Patient Preferred Adherence*, 2012, 6, 555-563
- [32] Hatala R., Pella D., Hatalova K., Sidlo R., Optimisation of blood pressure treatment with fixed-combination perindopril/amlodipine in patients with arterial hypertension, *Clin Drug Invest.*, 2012, 32(9), 603-612
- [33] Punzi H., Shojaei A., Maa J.F.; on behalf of the BP-CRUSH Investigators., Efficacy and tolerability of fixed-dose amlodipine/olmesartan medoxomil with or without hydrochlorothiazide in Hispanic and non-Hispanic patients whose blood pressure is uncontrolled on antihypertensive monotherapy, *Ther Advr Cardiovasc Dis.*, 2012, 6(4), 149-161
- [34] McGibney D., The efficacy of amlodipine in the management of ischaemic heart disease, *Postgrad Med J.*, 1991, 67 Suppl 3, S24-28
- [35] Palma-Gámiz J.L., High blood pressure and calcium antagonism, *Cardiology*, 1997, 88 Suppl 1, 39-46
- [36] Ishimitsu T., Minami J., Yashii M., Suzuki T., Inada H., Ohta S., et al., Comparison of the effects of amlodipine and losartan on 24-hour ambulatory blood pressure in hypertensive patients, *Clin Exp Hypertens.*, 2002, 24(1-2), 41-50
- [37] Ajayi A.A., Akintomide A.O., The efficacy and tolerability of amlodipine and hydrochlorothiazide in Nigerians with essential hypertension, *J Natl Med Assoc.*, 1995, 87(7), 485-488
- [38] Sasaguri M., Matsumoto N., Noda K., Koga M., Kinoshita A., Ideishi M., et al., Amlodipine lowers blood pressure without increasing sympathetic activity or activating the renin-angiotensin system in patients with essential hypertension, *Eur J Clin Pharmacol.*, 1997, 53(3-4), 197-201
- [39] Mroczek W.J., Burris J.F., Klein J., A double-blind evaluation of the effect of amlodipine on ambulatory blood pressure, *Postgrad Med J.*, 1991, 67 Suppl 5, S24
- [40] Abernethy D.R., Pharmacokinetics and pharmacodynamics of amlodipine, *Cardiology*, 1992, 80 Suppl 1, 31-36
- [41] Naidu M.U., Usha P.R., Rao T.R., Shobha J.C., et al., Evaluation of amlodipine, lisinopril and a combination in the treatment of essential hypertension, *Postgrad Med J.*, 2000, 76(896), 350-353
- [42] Hagar J.M., Newman L.G., Kloner R.A., Effects of amlodipine on myocardial infarction, infarct expansion and ventricular geometry in the rat, *Am Heart J.*, 1992, 124(3), 571-580
- [43] Milovanovic B., Trifunovic D., Milicevic N., Vasic K., Krotin M., The significance of amlodipine on autonomic nervous system adjustment (ANSA method): a new approach in the treatment of hypertension, *Srp Arh Celok Lek.*, 2009, 137(7-8), 371-378
- [44] Mancia G., Omboni S., Zanchetti A., Clinical advantages of lipophilic dihydropyridines, *Blood Press Suppl.*, 1998, 2, 23-26
- [45] Siché J.P., Baquet J.P., Faquet P., Trémel F., de Gaudemaris R., Mallion J.M., Effects of amlodipine on baroreflex and sympathetic nervous system activity in mild-to-moderate hypertension, *Am J Hypertens.*, 2001, 14(5Pt1), 424-428
- [46] Lund-Johansen P., Omvik P., White W., Digrones O., Helland B., Jordal O., et al., Long-term haemodynamic effects of amlodipine at rest and during exercise in essential hypertension, *Postgrad Med J.*, 1991, 67 Suppl 5, S20-23
- [47] Huraib S., Askar A., Abu-Aisha H., Al-Wakeel J., Mitwalli A., Al-Majed S., et al., Efficacy of once-daily amlodipine in the control of 24-hour blood pressure using ambulatory blood pressure monitoring, *Curr Therap Res.*, 1995, 56(11), 1125-1131
- [48] Khong S.M., Andrews K.L., Huynh N.N., Venardos K., Aprico A., Michell D.L., et al., Arginase II inhibition prevents nitrate tolerance, *Br J Pharmacol.*, 2012, 166(7), 2015-2023
- [49] Fox K., Garcia M.A., Ardissino D., Buszman P., Camici P.G., Crea F., et al., Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology, *Eur Heart J.*, 2006, 27(11), 1341-1381
- [50] Meredith P.A., Therapeutic implications of drug "holidays", *Eur Heart J.*, 1996, 17 Suppl A, 21-24
- [51] Ongtengco I., Morales D., Sanderson J., Lu Z.R., Beilin L.J., Burke V., et al., Persistence of the antihypertensive efficacy of amlodipine and nifedipine GITS after two "missed doses": a randomised, double-blind comparative trial in Asian patients, *J Hum Hypertens.*, 2002, 16(11), 805-813
- [52] Mehta J.L., Lopez L.M., A double-blind evaluation of amlodipine in patients with chronic, stable angina: sustained efficacy and lack of "withdrawal phenomenon" upon abrupt discontinuation, *Clin Cardiol.*, 1994, 17(9 Suppl 3), III17-22
- [53] Gorwit J., Haidet G.C., Russell D.C., Tonkon M., Deedwania P.C., Borer J.S., Randomised Placebo-Controlled Withdrawal Study of amlodipine in Angina Pectoris, *Am J Ther.*, 1995, 2(1), 34-42
- [54] Koracevic G., Significance of "beta blocker rebound phenomenon" and new suggestions how to avoid it, *Proceedings of the World Medical Conference, WSEAS* (26-28 September 2011, Prague, Czech Republic), Prague, 2011, 79-84
- [55] Chrysant S.G., Chrysant G.S., The pleiotropic effects of phosphodiesterase 5 Inhibitors on function and safety in patients with cardiovascular disease and Hypertension, *J Clin Hypertens.*, 2012, 14(9), 644-649
- [56] Webb D.J., Freestone S., Allen M.J., Muirhead G.J., Sildenafil citrate and blood-pressure-lowering drugs: results of drug interaction studies with an organic nitrate and a calcium antagonist, *Am J Cardiol.*, 1999, 4, 83(5A), 21C-28C